The Rejection of Claims 11, 14-19, 21, 22, 25, and 56 Under 35 U.S.C. §103(a)

Claims 11, 14-19, 21, 22, 25, and 56 are rejected as unpatentable over Miyawaki[1] in view Jin[2]. This rejection is respectfully traversed.

Claims 11, 14-19, 21, 22, 25, and 56 are directed to functional heterotrimeric G proteins which are capable of fluorescence energy resonance transfer (FRET). Upon G-protein coupled receptor (GPCR) signaling, conformational changes can be detected in the G proteins by detecting a change in FRET. See specification at page 8, lines 11-13.

Miyawaki is cited for teaching a very different fusion protein or pair of fusion proteins which are capable of FRET. Miyawaki teaches either two separate or a fused calmodulin and M13 proteins. Upon binding of calcium to calmodulin, a change in FRET is observed.

Jin is cited as teaching the interaction of G_{α} subunit with $G_{\beta\gamma}$ heterodimer to form a heterotrimer. Jin is silent with respect to FRET.

The PTO asserts that it was *prima facie* obvious that one of skill in the art could make functional heterotrimeric G proteins that are capable of FRET. Even if true, *arguendo,* the claimed functional heterotrimeric G proteins have an unexpected property which rebuts the asserted *prima facie* case. Unexpectedly and unpredictably, upon ligand binding to a G-protein coupled receptor *in vivo*, a change in FRET is observed in the heterotrimeric G-protein. Prior to the making of the claimed proteins, there was simply no way to know if a change in conformation of the heterotrimeric G-protein would occur under such circumstances. And if the change did occur, there was no way to know if it would be sufficient to effect a change in FRET of the fusion proteins.

The specification at Example 3 teaches that the addition of chemoattractant cAMP to cells which carry a heterotrimeric G protein which was capable of FRET, triggered a rapid, substantial loss of FRET. Results are shown in Figure 2. Previous studies of the interactions of the heterotrimeric G protein subunits were performed on isolated proteins *in vitro.* There was simply no way to know that the requisite changes to FRET would occur *in vivo* in whole cells.

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1 *Nature, 388:* 882-887, 1997.
2 *Mol. Biol. Cell, 9:* 2949-2961, 1998.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. §2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). The present rejection fails to make a *prima facie* case because there was no reasonable expectation of success.

The Final Office Action asserted that it would have been obvious that heterotrimeric G proteins would be able to display FRET. Applicants previously pointed out that the heterotrimeric G protein system is far more complex than the calmodulin/M13 system of Miyawaki, because to be functional, G protein subunits have to retain enzymatic activity, interact with each other, and interact with GPC receptors. Thus, Applicants argued, one of ordinary skill in the art would not have had a reasonable expectation of success based on Miyawaki. The Final Office Action asserted that success was, in any event, predictable because Miyawaki taught that GFP "cDNA can be concatenated with those encoding many other proteins, and the resulting fusion proteins are ***usually*** fluorescent and ***often*** preserve biochemical functions and cellular localization of the partner proteins." Miyawaki at page 882, col. 2, lines 24-27; emphasis added. Such a statement, however, is simply insufficient to lead to a reasonable expectation of success that heterotrimeric G proteins would retain their many required biochemical functions. One of ordinary skill in the art simply could not have predicted that one could make fusion proteins with the G protein subunits and retain enzymatic activity (GTPase activity), retain the ability to heteroöligomerize (*i.e.*, α, β, and γ subunits), and retain the ability to "be activated" by receptor signaling. Retention of these many functions clearly could not have been predicted based on the prior art teachings, including Miyawaki's statement that fusion proteins "often" preserve biochemical functions.

The Final Office Action also cites Miyawaki as teaching that "FRET is a non-destructive method," implying that the making of fluorescent fusion proteins would not destroy the protein function. However, what Miyawaki actually taught is that "FRET is a non-destructive spectroscopic method," which means that the excitation of proteins that display FRET and observation of emitted light from FRET do not destroy the cells. Thus this statement of Miyawaki does not support the PTO's contention that the retention of heterotrimeric G protein function after fusion to fluorescent moieties was predictable.

Withdrawal of the rejection is therefore requested.

The Rejection of Claims 13, 77-86, 89, 91-93 Under 35 U.S.C. §103(a) and

The Rejection of Claims 20, 23-24, 87-88, and 90 Under 35 U.S.C. §103(a)

Claims 13, 77-86, 89, 91-93 are rejected as unpatentable over Miyawaki in view of Jin and further in view of Xu. Claims 20, 23-44, 87-88, and 90 are rejected as unpatentable over Miyawaki in view of Jin and further in view of Medina and Wall. These rejections are respectfully traversed.

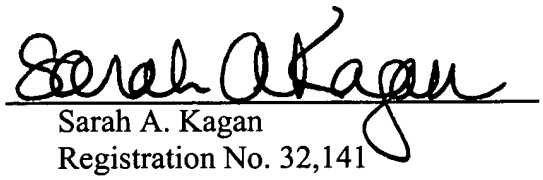
Each of the tertiary references, Xu, Medina, and Wall, is cited to demonstrate a feature found in one of the rejected claims, including the use of a distance of 100 angstroms between FRET moieties and the use of BRET instead of FRET. However, none of the tertiary references remedies the deficiencies of Miyawaki and Jin in making a *prima facie* case. None of the tertiary references rebuts the unexpected result that the claimed functional heterotrimeric G proteins demonstrate a change in FRET/BRET upon stimulation of a G protein coupled receptor. Thus, for the very same reasons as outlined above with respect to claims 11, 14-19, 21, 22, 25, and 56, claims 13, 20, 23-24, and 77-93 are also patentable. The cited prior art gave no reasonable expectation of success that the claimed proteins would retain their functionality while demonstrating FRET or BRET, and even if *arguendo* it did, the decrease in FRET/BRET upon ligand binding to a G protein coupled receptor was not predictable.

Withdrawal of this rejection is respectfully requested.

A speedy allowance of all pending claims is respectfully requested.

Respectfully submitted,

Date: September 6, 2005

By: 

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